Review

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The diagnosis and treatment of idiopathic pulmonary fibrosis

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrosing interstitial lung disease (ILD) of unknown cause. The prognosis of IPF is poor, respiratory failure is the most common cause of mortality. Velcro rales are typical on respiratory system examination. Clubbing is seen in 30-60% of IPF cases. There is no laboratory test specific to IPF. Usual interstitial pneumonia (UIP) pattern is seen in IPF. UIP features in high-resolution computed tomography (HRCT); peripheral subpleural bibasilar reticular opacities, honeycombing, traction bronchiectasis and interseptal thickening. It shows craniocaudal localization. Diagnosis of IPF; It is diagnosed by the combination of HRCT findings and clinical findings. Antifibrotic drugs (Pirfenidone and Nintedanib) slow down the progression of IPF and reduce the number of annual attacks and reduce the frequency of hospitalization.

Keywords: Idiopathic pulmonary fibrosis, usual interstitial pneumonia, antifibrotic drugs

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrosing interstitial lung disease (ILD) of unknown cause. It leads to rapid and progressive alterations in lung function. IPF has a poor prognosis, with an average life expectancy of 3-5 years from diagnosis if left untreated. The mortality rate is higher than that of many malignancies.

IPF is uncommon in people under 50 years of age. Both prevalence and incidence rise with increasing age, with presentation commonly occurring in the sixth and seventh decades.[1]

The prevalence and incidence rates of IPF are increasing worldwide. it is more common in men.[2]

IPF is still a rare disease with a recent global incidence of 0.09–1.30 and a prevalence of 0.33-4.51 per 10,000 of the population.[3]

PATHOGENESIS AND GENETIC PREDISPOSITION

It is well recognized that the combination of environmental and genetic risk factors leads to the development of IPF. The alveolar epithelium is predominantly impacted by repetitive microdamages. An abnormal healing process begins after epithelial damage. Accumulation of myofibroblast, fibroblast, and collagen is brought on by an imbalance between fibrotic and anti-fibrotic mediators. Following that, fibrosis, honeycomb cysts, and tissue degeneration happen.[4]

While there have been reports of familial cases, the majority of IPF cases are sporadic.

Familial IPF is defined as IPF in at least two of the primary biological family members. Familial IPF; It is seen at a rate of 0.5-2.2%.[5]

It is autosomal dominant and is observed at earlier ages.

Short telomere syndromes, Hermansky-Pudlak syndrome, and familial pulmonary fibrosis (FPF) all typically manifest earlier than IPF. While some genetic variants have been identified in people with sporadic IPF, none are well-established.

Telomere shortening, decreased mucociliary clearance due to MUC5B, surfactant protein changes and TOLLIP mutation are genetic changes detected in IPF.

POTENTIAL RISK FACTORS

There are some risk factors that cause the development of the IPF. These factors are male gender, age, smoking history over 20 pack/year, environmental and occupational factors, chronic micro-aspirations because of gastroesophageal reflux and viral factors.[6]

The study in the USA identified some occupations associated with the IPF. These professions agriculture,

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animal husbandry, hairdressing, bird breeding, stone cutting and polishing are occupations that are exposed to metal dust and vegetable dust.[6]

CLINICAL MANIFESTATIONS

The most common IPF symptoms are nonproductive cough and exertional dyspnea. Generally, the first symptom is a dry cough. Cough is a symptom that reduces quality of life and is difficult to manage. It is more prevalent, particularly among nonsmokers and those with severe disease. Fever, weight loss, and muscle and joint pain are uncommon.

It is important to ask detailed questions about the patient's past smoking, family history,hobbies, exposure to the environment and their job, and drug usage during their anamnesis. It is important to do a systemic examination, particularly in cases with signs or symptoms of rheumatic disease (Table 1).[7]

Table 1. Questions for patient with suspected idiopathic pulmonary fibrosis (IPF)[7]

Tobacco use
• Do you smoke tobacco now or have you in the past? If yes, how many packs per day and how many years?
Symptoms of rheumatic disease/sarcoidosis
• Do you have joint pain or inflammation, digital ulcers, dry eyes, dry mouth, fatigue, fever, hair loss, muscle weakness or pain, photosensitivity, Raynaud phenomenon, skin changes such as thickening or telangiectasia? • Any new rash, particularly around tattoos or scars? • Any palpitations or fainting episodes? • Any parotid swelling?
Exposures associated with hypersensitivity pneumonitis
• Do you have pets or birds at home? How about livestock? • Any exposure to humidifiers, hot tubs, sauna, Jacuzzi, feather bedding, wind instruments, barns? • Any water damage at home or at work? • What are your hobbies? Do they involve exposure to dusts, feathers, fur, mold, fumes, or chemicals?
Occupational causes of ILD
• What types of work have you had? Any exposure to animals, stables or barns, mushroom growing, brewery, winery, asbestos, silica, plastics, epoxy, metalworking, spray painting, sandblasting?
Medication and radiation-induced lung toxicity
• What medications do you take? Have you ever taken nitrofurantoin, amiodarone, chemotherapy, or biologic agents? Have you had radiation therapy? If so to what part of the body?
Family history
• Do you have any family history of lung disease, particularly ILD or lung fibrosis? Any history of premature graying, cirrhosis, aplastic anemia, other bone marrow diseases?

Adapted from Reference 7, IPF: idiopathic pulmonary fibrosis; ILD interstitial lung disease.

On physical examination, bibasilar crackles are usually audible. However in rare cases, they may be absent or only heard unilaterally in the early stages of the disease. Due to traction bronchiectasis, patients with more advanced illness may experience end-inspiratory "squeaks".

Clubbing is practiced at a rate of 30-60% in IPF.

In our country, the rate of clubbing was determined to be 36.4% in a study.[8]

Hypoxemic patients may develop right heart failure and pulmonary hypertension. Examination signs such as jugular vein distention, pretibial edema, and hepatomegaly are observed in these instances.

LABORATORY

As there are no specific laboratory tests for the diagnosis of IPF, the purpose of laboratory testing in patients who have just been diagnosed with ILD is to determine which processes to rule out or identify as part of the differential diagnosis.

Serologic investigations may be useful in identifying subclinical rheumatic disease in patients undergoing an initial evaluation for possible IPF.

Antinuclear antibodies, anticyclic citrullinated peptide antibodies, and rheumatoid factor tests are usually obtained. Certain experts obtain the nonspecific measures of inflammation, such as erythrocyte sedimentation rate and creactive protein (CRP).

Additional tests, like creatine kinase, aldolase, Sjögren's antibodies (anti-SS-A, anti-SS-B), scleroderma antibodies (anti-topoisomerase [SCL-70], anti-PM-1), and other myositis panel antibodies (e.g., anti-Jo-1, anti-PL7, anti-melanoma differentiation associated gene 5 [MDA-5]), may be useful in some cases with suggestive symptoms or signs.[9]

Some biomarkers that are believed to be useful in forecasting the disease's prognosis have been developed recently. These biomarkers include antigens such as endothelin-1, matrix metalloproteinases like MMP-7 and MMP-1, surfactant proteins A and D, and KL-6. It hasn't been used on a regular basis yet.

PULMONARY FUNCTION TESTS

While pulmonary function tests (PFT) are normal in the early stages, restrictive disorder develops later. Total lung capacity, functional residual capacity, and residual volume all decrease, resulting in impaired compliance. The FEV1/FVC ratio (Tiffenau ratio) remains constant as forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) decrease. When an airway disease is present, both restrictive and obstructive patterns can be seen.

Diffusion capacity (DLCO) has decreased as an indicator of gas exchange disorder, and it is the first parameter to deteriorate. While the DLCO/VA ratio remains constant, the decrease in DLCO is a significant finding that differentiates it from obstructive diseases.

During cardiopulmonary exercise testing, the alveolar-arterial oxygen gradient ($P(A\text{-}a)O_2$) rises while arterial oxygen pressure and saturation fall. The six-minute walk test (6MWT) is a noninvasive, easily applied test that assesses patients' functional exercise capacity. In patients with IPF, the distance walked and desaturation measured during the 6MWT are strong predictors of mortality.

CHEST IMAGING

Chest Radiography

The most common finding in IPF is an increase in reticular markings, though this is a nonspecific finding that is also associated with other ILDs and heart failure.

High-resolution Computed Tomography

All patients suspected of having IPF should have an HRCT. The "Usual interstitial pneumonia (UIP) pattern" is seen in the IPF. That is distinguished by peripheral, basilar-predominant opacities associated with honeycombing and traction bronchiectasis-bronchiolectasis on HRCT. It shows craniocaudal location (**Figure 1**).

Both definite UIP and probable UIP patterns on HRCT show histopathologic confirmation of UIP greater than 80 percent of the time.[7]

The 2022 Idiopathic Pulmonary Fibrosis and Progressive Pulmonary Fibrosis ATS/ERS/JRS/ALAT Adult Clinical Practice Guidelines.[10]

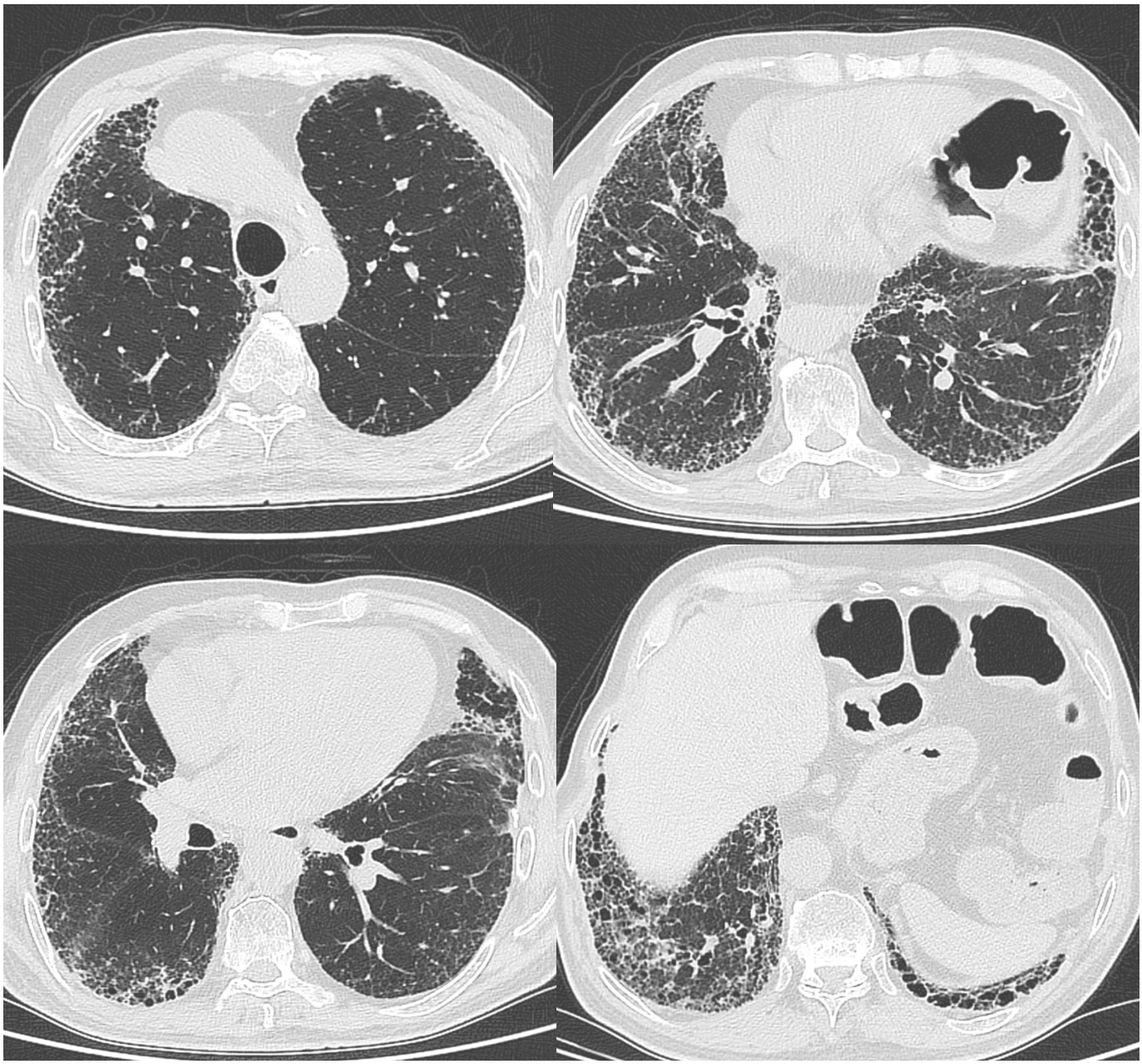


Figure 1. Usual interstitial pneumonia (UIP) pattern at High-resolution computed tomography (HRCT)

Review HRCT model categories. The 2018 guideline considered merging UIP diagnoses with probable UIP, but it was ultimately decided to keep the four categories with minor changes (Table 2).

HISTOPATHOLOGY

Histopathological diagnosis of IPF; patchy interstitial fibrosis, which causes roof damage in the lung, is diagnosed with the appearance of UIP consisting of honeycomb and fibroblastic focus. The main feature of fibrosis is that it is histologically heterogeneous. The pathological diagnostic criteria in the 2018 IPF guideline9 are summarized in Table 3.

DIAGNOSIS

A characteristic presentation (such as the gradual onset of dyspnea in a patient over 60,) combined with characteristics of usual interstitial pneumonia (UIP) or probable UIP on high-resolution computed tomography (HRCT) can often lead to the diagnosis of IPF without the need for a biopsy.

Diagnosis of IPF; It is diagnosed by the combination of HRCT findings and histopathological findings (Figure 2).

Other known causes of radiographic UIP must be clinically excluded, including environmental exposures (e.g., asbestos, causes of hypersensitivity pneumonitis), medications, and rheumatic disease

To reach histopathological diagnosis, diagnostic methods such as Bronchoalveolar Lavage (BAL), transbronchial biopsy, transthoracic biopsy, transbronchial cryobiopsy, endobronchial ultrasonographyguided fine needle aspiration, video-guided thoracoscopic surgery (VATS), and surgical biopsy are preferred. Bronchoalveolar lavage (BAL) has a limited role in the evaluation of patients with an HRCT that suggests IPF and it is used to differantiate other causes (such as sarcoidosis, hypersensitivity pneumonitis)

Surgical lung biopsies should ideally be obtained from multiple lobes of the lung and from areas of varying severity. When inflated, lung biopsy samples should be larger than 4 cm in the greatest dimension and 3 to 5 cm deep from the pleural surface.[7]

Transbronchial cryobiopsy (TBCB), when performed in centers with multidisciplinary experience in the diagnosis and treatment of ILD, is a suitable substitute for surgical lung biopsy.

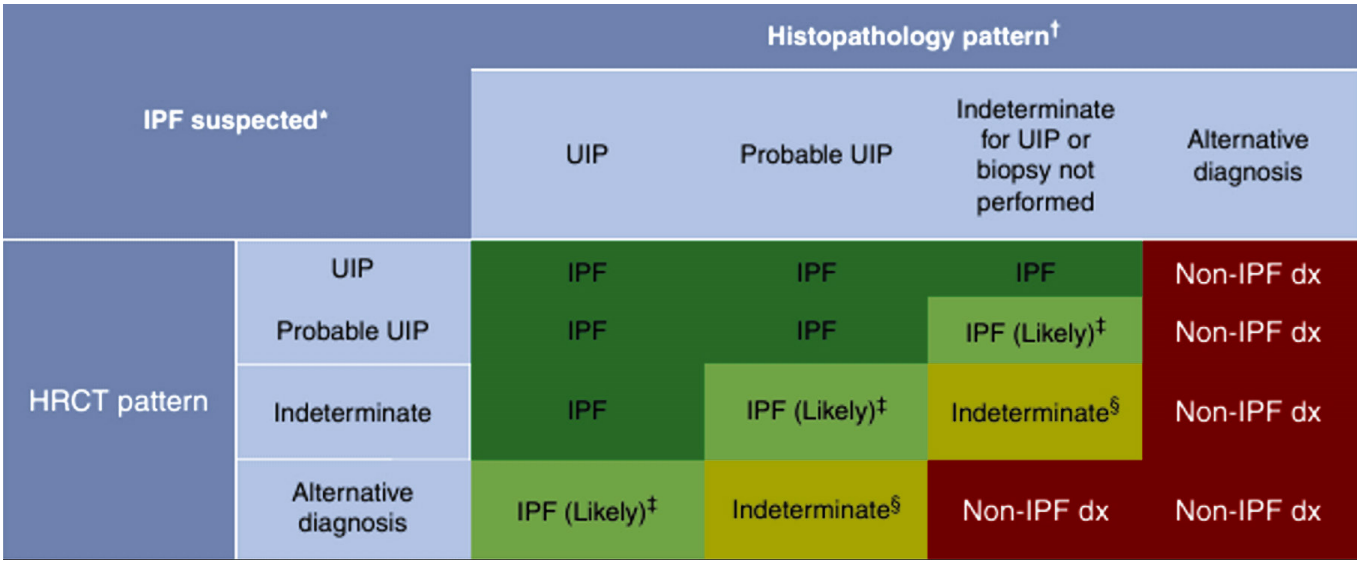
Table 2. High-resolution computed tomography patterns in idiopathic pulmonary fibrosis[10]

	UIP	Probable UIP	Indeterminate UIP	Alternative Diagnosis
Confidence level	90%	70-89%	51-69%	<50%
Distribution	• Basal and subpleural dominance • Heterogeneous distribution • Diffuse distribution • It is possible to be asymmetrica	• Basal and subpleural dominance • Heterogeneous distribution	• Diffuse distribution without subpleural predominance • Indeterminate reticulation, • slight groundglass or distortion (Early UIP)	• Peribronchovascular prednominance and sub-plaveral prevention (NSIP) • Perilymphatic (sarcoidosis) • Upper and middle zone involvement (fibrotic HP, CTD-ILD, sarcoidosis) • Sub-plveral prevention (NSIP or smoking-associated ILD)
HRCT view	• Honeycomb and/or peripheral traction bronchiectasis or bronchiolectasis • Presence of irregular thickening of the interlobular septa • Generally reticular pattern superimpose, slightly ground-glass • There may be pulmonary ossification	• Peripheral traction bronchiectasis or bronchiectasis with reticular pattern • Possible to have moderate frosted glass • Absence of subpleural involvement	• Pulmonary fibrosis distribution (if not suggestive of any specific etiology)	Lung findings • Cysts (LAM, LCH, LIP, DIP) • Mosaic attenuation, three density hulgus (HP) • Common ground-glass (HP, cigarette-related illicit drug toxicity, fibrotic acute attack) • Diffuse nodules (sarcoidosis) • Centrilobular nodules (HP or non-associated disease) • Consolidation (OP) Mediastinal findings • Pleural plaque (asbestosis) • Dilated esophagus (CTD)

NSIP: Nonspecific Interstitial Lung Disease, HP: Hypersensitivity Pneumonia, LAM: Lymphangia Leio Myomatosis, LCH: Langerhans Cell Histiocytosis, LIP: Lymphocytic Interstitial Pneumonia, OP: Organized Pneumonia, ILD: Interstitial Lung Disease, UIP: Usual Interstitial Pneumonia, CTD: Connective Tissue Diseases

Table 3. Histopathological diagnostic criteria[9]

UIP	Probable UIP	Indefinite UIP	Alternative diagnoses
• Condense fibrosis causing structural damage • Subpleural and/or para-septal dominant distribution of fibrosis • Heterogeneous involvement of the parenchyma with fibrosis • Fibroblast foci • Absence of alternative diagnostic findings	• Some of the features of the UIP pattern are present but not sufficient to diagnose UIP and there are no alternative diagnostic findings or • Only honeycombing	• Fibrosis with/without structural damage • Non-UIP pattern or features of UIP due to secondary causes • Some of the features of the UIP pattern are present and there are findings suggesting an alternative diagnosi	• Other histological patterns of idiopathic interstitial pneumonias in all biopsies • Histological findings pointing to other diseases (such as HP, PLHH, sarcoidosis, LAM



*"Clinically suspected of having IPF" is defined as unexplained patterns of bilateral pulmonary fibrosis on chest radiography or chest computed tomography, bibasilar inspiratory crackles,and age >60 years. Middle-aged adults (40 and 60year old) can rarely present with other wise similar clinical features, especially in patients with features suggesting familial pulmonary fibrosis.
‡IPF is the likely diagnosis when any of the following features are present:

1) Moderateto severe traction bronchiectasis and/or bronchiolectasis (defined as mild traction bronchiectasis and/or bronchiolectasis in four or more lobes, including the lingula as a lobe, or moderate to severe traction bronchiectasis in two or more lobes) in a man >50 years old or in a woman >60 years old,
2) Extensive (30%) reticulation on HRCT and age >70 year
3) İncreased neutrophils and/or absence of lymphocytosis in BAL fluid, and
4) Multidisciplinary discussion produces a confident diagnosis of IPF

§Indeterminate for IPF
1)without an adequate biopsy remains indeterminate and
2)with an adequate biopsy maybe reclassified to a more specific diagnosis after multidisciplinary discussion and/or additionalc onsultation.
Adapted from Reference 10, dx=diagnosis;UIP=usual interstitial pneumonia.

Figure 2. Idiopathic pulmonary fibrosis (IPF) diagnosis on the basis of high-resolution computed tomography (HRCT) and biopsy patterns10

The transbronchial cryobiopsy method was highlighted among the diagnostic methods in the Idiopathic Pulmonary Fibrosis and Progressive Pulmonary Fibrosis ATS/ERS/JRS/ALAT Clinical Practice Guidelines in Adults published in 2022.[10] Transbronchial cryobiopsy was found to have a lower risk of pneumothorax and bleeding than surgical lung biopsy.

DIFFERENTIAL DIAGNOSIS

Other diseases with radiographic and histopathologic features of typical interstitial pneumonia (UIP) are included in the differential diagnosis of IPF. Such as rheumatic diseases, chronic hypersensitivity pneumonitis, asbestosis, and certain drug-induced lung diseases.

Pleuropulmonary elastosis, pulmonary Langerhans' cell histiocytosis, combined pulmonary fibrosis and emphysema, and other idiopathic interstitial pneumonias are also included in the differential diagnosis of IPF. The interpretation of lung biopsy results in interstitial pneumonitis is discussed separately.

TREATMENT

There is no cure for IPF, but two antifibrotic drugs, nintedanib and pirfenidone, appear to slow disease progression and decrease the frequency of acute exacerbations. The use of anti-fibrotic drugs that prevent fibrosis in the lung parenchyma has been the most significant advancement in the treatment of IPF in recent years. The only definitive treatment is lung transplantation. New drug studies are still ongoing.

In our country, both drugs are within the scope of reimbursement, and patients who are diagnosed with IPF by lung biopsy or HRCT, in mild-to-moderate stages, with DLCO≥30%, FVC≥50%, are started. Anti-fibrotic drug selection should be made considering the patient's comorbid diseases, drugs used and contraindicated conditions.

One of the most important effects of pirfenidone is to alter the pleiotropic TGF-β pathway. Pirfenidone is used at a dose of 2400-2403 mg/day in the world and in our country. In our country, the drug is available as 200-400-600 mg tablets. The drug is started at a low dose (200 mg tablet 4x1), weekly hemogram and biochemistry values are checked and if the patient can tolerate it, the dose is increased and continued at the maximum dose (200 mg tablet 4x3 or 600 mgr 4x1) from the 15th day.

Skin rash, photosensitivity, and gastrointestinal (GI) side effects (nausea, vomiting, dyspepsia, loss of appetite, and diarrhea) are the most frequent side effects. All patients should be advised to wear sun protective clothing and sunscreen with at least a 50 factor in order to prevent skin side effects. It should be recommended to take drugs with meals and use proton pump inhibitors to prevent and reduce GI system side effects.

Nintedanib plays a role in the treatment of IPF by inhibiting multiple receptor tyrosine kinases (TKIs), including platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and vascular endothelial growth factor receptor (VEGFR).

There is only one form of nintedanib. 2x150 mg daily is started. Depending on the side effects seen in the patient, the nintedanib dose can be reduced by 2x100 mg. It should be used with caution in patients on anticoagulant therapy or with coronary artery disease.

The most common side effects are related to the gastrointestinal tract and the most common side effect is diarrhea. Antidiarrheal drugs added to the treatment of patients with diarrhea.

Hemogram and biochemistry values of patients using anti-fibrotic should be checked weekly in the first month of treatment, and then every three months.

There is no clear information on the treatment's duration. Patients should be evaluated every 3-6 months.

Supportive Therapy

Smokers should be referred to smoking cessation clinics, and psychosocial support should be provided as needed. Patients with respiratory failure should receive oxygen therapy support. Following a diagnosis, physicians should refer all patients to pulmonary rehabilitation centers. COVID-19, and seasonal influenza vaccination should be administered to patients on an annual basis and pneumococcal vaccine should be given. The treatment of comorbid diseases should be regulated. Patients at high risk of mortality should be referred for transplantation at the time of diagnosis, unless there are contraindications.

PROGNOSIS

The prognosis for IPF is poor. It is known that 20-30% of patients survive within five years of diagnosis, with an average life expectancy of two to five years.[1] The mortality rate has been reported at 13.36/100.000.[11] Respiratory failure is the most common cause of death.

CONCLUSION

IPF is a rare disease. Antifibrotic treatments, which have recently been used to slow the progression of the disease, have raised awareness. The disease's prognosis is altered by early diagnosis and treatment. New medical treatment options in IPF will increase diagnosis and awareness.

ETHICAL DECLARATIONS

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